Consumer and Corporate Affairs Canada | Consommation et Corporations Canada

(11) (A) No. 1 259 071

(45) ISSUED 890905

(52) CLASS 260-276.2
C.R. CL. 167-225;
260-277.7;
260-280.3;
260-306.05; 260-318

(51) INT. CL.[4] C07D 209/88, 401/12, 405/12

(19) (CA) **CANADIAN PATENT** (12)

(54) Process for the Preparation of Optically-Active Carbazole Derivatives, R- and S-Carbazole Derivatives and Pharmaceutical Compositions Containing These Compounds

(72) Leinert, Herbert,
Germany (Federal Republic of)

(73) Granted to Boehringer Mannheim G.m.b.H.
Germany (Federal Republic of)

(21) APPLICATION No. 454,948

(22) FILED 840523

(30) PRIORITY DATE (DE) Germany (Federal Republic of) (P 33 19 027.5) 830526

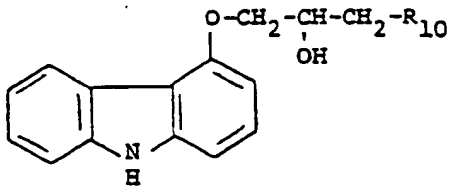
No. OF CLAIMS 42 - NO DRAWING

Canada

DISTRIBUTED BY THE PATENT OFFICE, OTTAWA.
CCA-274 (11-82)

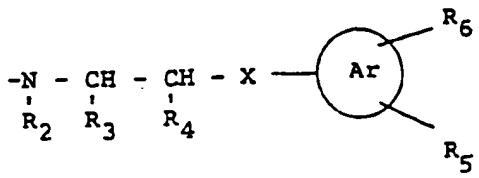
ABSTRACT OF THE DISCLOSURE

R-carbazole and S-carbazole derivatives are provided of the formula (I):



(I)

in which R_{10} is an unsubstituted or substituted amino radical and their pharmacologically compatible, pharmaceutically acceptable salts as well as processes for their preparation which permits production of the antipodes in pure form; the pharmacological effectiveness of the antipodes differ from that of the corresponging racemates and by selecting the ratio of R- and S-enantiomer the most favourable relationship of the different activities of the enantiomers can be obtained, pharmacological activity includes activity as ß-blockers and lowering of blood pressure.



in which R_2 is a hydrogen atom, a lower alkyl radical or a benzyl, phenylethyl or phenylpropyl radical, R_3 is a hydrogen atom or a lower alkyl radical, R_4 is a hydrogen atom or a lower alkyl radical, X a valency bond, a $-CH_2-$ group or an oxygen or sulphur atom, Ar is a phenyl naphthyl, indanyl, tetrahydronaphthyl or pyridyl radical and R_5 and R_6, which can be the same or different, are hydrogen or halogen atoms, lower alkyl radicals, aminocarbonyl groups, hydroxyl groups, lower alkoxy radicals, benzyloxy radicals, lower alkylthio radicals, lower alkylsulphinyl radicals or lower alkylsulphonyl radicals or together represent a methylenedioxy radical.

The lower alkyl radicals R_2, R_3, R_4, R_5 and R_6 and the lower alkoxy, lower alkylthio, lower alkylsulphinyl and lower alkylsulphonyl radicals R_5 and R_6 suitably have 1 to 6, and preferably 1 to 4, carbon atoms.

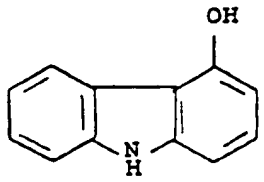
Compounds with the above-mentioned substituents R_{10} are described in Federal Republic of Germany Patent Specification No. 22 40 599 and in

reacted with ammonia or substituted ammonia of formula $R_{10}H$, in which R_{10} has the same meaning as above, whereafter the compound obtained is, if desired, converted into a pharmacologically compatible, pharmaceutically acceptable salt.

Substituted sulphonic acids in the definition of R_1 are, for example, methanesulphonic acid, p-toluenesulphonic acid and benzenesulphonic acid.

In particular the reaction is carried out in the presence of an organic solvent in an alkaline medium.

For convenience it is observed here that 4-carbazole has the formula:



The corresponding S-carbazole derivatives of formula (I) are obtained in similar manner. For this purpose, R-(-)-epichlorohydrin is first reacted with 4-hydroxycarbazole to produce S-4-(2,3-epoxypropoxy)-carbazole which is reacted with ammonia or a substituted amine of the formula $R_{10}H$, in which R_{10} has the same meaning as above, whereafter the

The preparation of the key compounds of general formula (II), preferably of the mesyl derivative, and of the R-(-)-epichlorhydrin are described in the literature (see Baldwin, J. org. Chem., 43, 4876/1978). According to this reference, D-mannitol is converted with acetone in the presence of zinc chloride into 1,2,5,6-di-O-isopropylidene-D-mannitol, splitting of which with sodium metaperiodate and subsequent immediate reduction of the intermediate aldehyde function formed gives S-(+)-isopropylidene-glycerol. Tosylation of this substance gives the R-3-tosyloxy-propanediolacetonide which, without isolation, is immediately converted into R-(-)-3-tosyloxy-1,2-propanediol. From this, by reaction with sodium methylate, there is obtained R-glycidol which, because of the danger of racemisation, is immediately reacted with methanesulphonyl chloride to give S-(+)-3-mesyloxy-1,2-epoxypropane.

For the preparation of the R-(-)-epichlorhydrin, S-(+)-3-mesyloxy-1,2-epoxypropane is opened with hydrochloric acid to give R-1-chloro-2-hydroxy-3-mesyloxypropane which, without purification, is reacted in ethylene glycol with sodium methylene-glycolate to give R-(-)-epichlorhydrin.

The two mentioned key substances are each reacted with 4-hydroxycarbazole, with reversal of the configuration, to give the previously unknown R-(-)-

favourable relationship of the two activity qualities can be objectively adjusted.

Example.

If, in the case of a racemate, the β-blockade, carried by the S-enantiomer, in comparison with the blood pressure lowering, carried by the R- and S-enantiomers, is too strong, then a more balanced activity relationship can be achieved by alteration of the proportion of the S-component.

Consequently, there can be used mixtures of R:S of from 1:99 to 99:1 except, in the meaning of the present invention, the ratio of 50:50 (racemate).

Experimental protocol

The β-blocking action was determined on awake rabbits on the basis of the inhibition of isoprenaline tachycardia (according to the method of Bartsch et al. (Experiments in animals on the pharmacological effects of metipranolol in comparison with propranolol and pindolol - Drug. Res., 27, (II), 12, 2319-2322/1977).

As a measure for the β-blocking activity strength, there was calculated the 50% inhibiting dosage.

Vasodilation (measured as direct blood pressure lowering after a single administration).

In awake, spontaneously hypertonic rats (SHR), catheters were implanted in the arteria femoralis and the vena jugularis. Via the veins, there were

TABLE

Action of R- and S-carvedilol on the heart (β-blockade) and blood vessels (blood pressure)

purity %	β-blockade		vasodilation	
	r	ED_{50} % (mcg/kg i.v.)	r	ED_{-30} mm Hg (mcg/kg i.v.)
R-carvedilol (> 99.4%)	0.96	3980	0.97	2960
S-carvedilol (> 99.4%)	0.99	25	0.96	270
relationship $\frac{R}{S}$	-	160	-	11

carvedilol = (1-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)]-ethylaminopropan-2-ol; racemate

In this specification, it will be understood that the qualification that the salts are "pharmaceutically acceptable" means that the salts have the necessary physical characteristics, for example, stability, to render them suitable for formulation into pharmaceutical compositions. The qualification that the salts be "pharmacologically compatible" is to be understood as extending to salts with non-toxic inorganic or organic acids which have no adverse effects to the extent that such salts would be unsuitable for administration to living bodies.

Salts of compounds of formula (I) which are not pharmaceutically acceptable and pharmacologically compatible form a useful aspect of the invention of the novel derivatives, inasmuch as they can be readily converted to different salts having the required physical and chemical characteristics to make them suitable for administration in pharmaceutical compositions to living bodies.

For the conversion of the compounds of formula (I) into their pharmacologically compatible, pharmaceutically acceptable salts, these are reacted, preferably in an organic solvent, with the equivalent amount of an inorganic or organic acid, for example hydrochloric acid,

especially a polyethylene glycol, polyvinylpyrrolidone or glycerol. As buffers, it is preferable to use acetic acid/sodium acetate, citric acid/sodium citrate or sodium EDTA.

The compounds of general formula (I) according to the present invention and their salts can be administered enterally or parenterally in liquid or solid form. As injection medium, water is preferably used which contains the additives usual in the case of injection solutions, such as stabilising agents, solubilising agents or buffers. Such additives are, for example, tartrate and citrate buffers, ethanol, complex formers (such as ethylenediamine-tetraacetic acid and its non-toxic salts) and high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials are, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high molecular weight fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycols). Compositions suitable for oral administration can, if desired, contain flavouring and sweetening materials.

The following Examples are given for the purpose of illustrating the present invention:

temperature, the mannitol thereby going into solution. The reaction mixture is filtered with suction, the filter residue is washed with a little dry acetone and the solution is immediately added, with stirring, to a mixture of 570 g. potassium carbonate, 600 ml. water and 1700 ml. diethyl ether. Precipitated zinc carbonate is filtered off and the filtrate is evaporated. The residue is taken up in methylene chloride and the water still present is separated off. Subsequently, the methylene chloride solution is dried over anhydrous sodium sulphate, treated with fuller's earth (floridin) and substantially evaporated. 3 Litres cyclohexane are then added thereto and left to crystallise. For further purification, the residue is again recrystallised from cyclohexane. Yield: 200 g. 1,2,5,6-di-O-isopropylidene-D-mannitol: m.p. 120 - 121°C.

b) S-(+)-Isopropylidene-glycerol

To a solution of 199 g. sodium metaperiodate in 1680 ml. water is added portionwise, with stirring and ice cooling, in the course of 45 minutes, 244 g. 1,2,5,6-di-O-isopropylidene-D-mannitol. After the addition is complete, stirring is continued for 15 minutes and then 5 litres ethanol are added thereto. The reaction mixture is filtered off with suction, the filter residue is then washed with ethanol and the filtrate is mixed, with slight cooling, in the

solution, dried over anhydrous sodium sulphate, treated with floridin and evaporated. There are obtained 69.1 g. of an oily residue of R-3-tosyloxy-propanediol acetonide which, without further purification, is further reacted. The acetonide is warmed to 80°C. in a mixture of 50 ml. acetone and 147 ml. 1N hydrochloric acid for 40 minutes, a clear solution being obtained. The solution is evaporated in vacuo and the residue is dissolved in methylene chloride. The methylene chloride solution is dried over anhydrous sodium sulphate and evaporated. The residue is recrystallised from diisopropyl ether. Yield: 45 g. R-(-)-3-tosyloxypropane-1,2-diol: m.p.: 62°C.; $[\alpha]_D^{20}$: -9.9° (c = 7.9; methanol): $[\alpha]_D^{20}$: -6.8° (c = 7.5; pyridine).

d) <u>R-Glycidol</u>

45 g. R-(-)-3-Tosyloxypropane-1,2-diol are dissolved in a mixture of 40 ml. anhydrous methanol and 75 ml. anhydrous diethyl ether. To this is added dropwise, with stirring, at 0 to 5°C., within the course of 20 minutes, a solution of 4 g. sodium in 90 ml. methanol. The reaction mixture is further stirred for 2 hours and filtered off with suction. The filter residue is washed with diethyl ether and the filtrate is evaporated in vacuo at a bath temperature of 20°C. The residue is again taken up in diethyl ether and the solution treated with floridin,

this temperature. There are thus obtained 15.7 g. R-(-)-epichlorhydrin; yield: 78%; $[\alpha]_D^{20}$: -33.8° (c = 1, methanol).

Example 3.

S-(+)-4-(2,3-Epoxypropoxy)-carbazole

27.5 g. 4-Hydroxycarbazole are dissolved in a mixture of 150 ml. 1N aqueous sodium hydroxide solution and 70 ml. dimethyl sulphoxide. To this is added at ambient temperature 13.9 g. R-(-)-epichlorhydrin, followed by stirring for 18 hours at ambient temperature. 280 ml. Water are then added thereto, followed by stirring for 15 minutes and filtering off with suction. The filter residue is washed with 0.1N aqueous sodium hydroxide solution and water and subsequently dissolved in methylene chloride. The methylene chloride solution is dried over anhydrous sodium sulphate, treated with active charcoal and floridin and evaporated. The residue is purified by recrystallising twice from ethyl acetate. Yield: 15.2 g. S-(+)-4-(2,3-epoxypropoxy)-carbazole; m.p.: 163 - 164°C.; $[\alpha]_D^{20}$: +64.4° (c = 1; pyridine).

From the mother liquors, there are isolated a further 6.7 g. of product; m.p.: 163 - 164°C.; $[\alpha]_D^{20}$: +64.5° (c = 1, pyridine).

Example 4.

R-(-)-4-(2,3-Epoxypropoxy)-carbazole

21.9 g. 4-Hydroxycarbazole are dissolved in a

glacial acetic acid. Upon cooling, S-(-)-carbazole hydroacetate crystallises out. The precipitate is filtered off, washed with ethyl acetate and dried. Yield: 410 mg.; m.p.: 158 - 160°C.; $[\alpha]_D^{20}$: -20.1° (c = 1; glacial acetic acid); optical purity according to gas chromatography findings: 99.5%.

Example 6.

R-(+)-(1-Carbazol-4-yloxy)-3-isopropylaminopropan-2-ol hydroacetate

18 g. R-(-)-4-(2,3-Epoxypropoxy)-carbazole are dissolved in 140 ml. methanol and, after the addition of 100 ml. isopropylamine, the solution is heated to 65°C. for 2 hours. The solution is then evaporated to dryness, further dried for 1 hour in high vacuum for the removal of residual isopropylamine and the residue is dissolved in 300 ml. hot ethyl acetate. The ethyl acetate solution is treated with floridin and, after suction filtration, mixed while still hot with 8.6 ml. glacial acetic acid. After cooling, the precipitated crystals are filtered off with suction. For further purification, the crystals are recrystallised from ethyl acetate, with the addition of a little methanol. Yield: 23 g. R-(+)-(1-carbazol-4-yloxy)-3-isopropylaminopropan-2-ol hydroacetate; m.p.: 158 - 160°C.; $[\alpha]_D^{20}$: +20.2° (c = 1; glacial acetic acid): optical purity: 98.6%; chemical purity: 99.97%.

The patent specifications referred to herein are more particularly identified below:

Federal Republic of Germany Patent Specification No. 22 40 599, published October 16, 1975, Herbert Leinert et al, assigned to Boehringer Mannheim GmbH.

European Patent Specification 0,004,920 published August 5, 1981, Fritz Wiedemann et al, assigned to Boehringer Mannheim GmbH.

hydroxyl groups, lower alkoxy radicals, benzyloxy radicals, lower alkylthio radicals, lower alkylsulphinyl radicals or lower alkylsulphonyl radicals or together represent a methylenedioxy radical.

or a pharmaceutically acceptable, pharmacologically compatible salt thereof, which comprises:

reacting R- or S-4-(2,3-epoxypropoxy) carbazole with a compound of formual (III):

$$R_{10}H \qquad (III)$$

in which R_{10} is said amino or substituted amino radical and,

when desired, converting the R- or S-carbazole derivative (I) obtained to a corresponding pharmaceutically acceptable, pharmacologically compatible salt thereof.

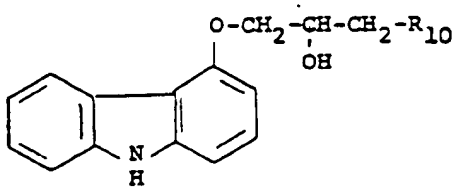
6. A process according to claim 3, wherein said compound (III) is ammonia.

7. A process according to claim 1, wherein said compound (III) is isopropylamine, tert. butylamine or o-methoxyphenoxyethylamine.

8. A process according to claim 2, wherein said compound (III) is isopropylamine, tert.butylamine or o-methoxyphenoxyethylamine.

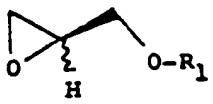
9. A process according to claim 3, wherein said compound (III) is isopropylamine, tert.butylamine or o-methoxyphenoxyethylamine.

10. A process for the preparation of an R-carbazole derivative of formula (I):



(I)

in which R_{10} is an amino group or an amino group substituted by a lower alkyl radical, or is the radical:



(II)

in which R_1 is the residue of a substituted sulphinic acid derivative, with 4-hydroxycarbazole in the presence of an organic solvent in an alkaline medium, and

reacting the R-4-(2,3-epoxypropoxy)-carbazole obtained with ammonia or substituted ammonia of the formula $R_{10}H$, in which R_{10} has the same meaning as above, whereafter the compound (I) obtained is, if desired, converted into a corresponding pharmacologically compatible, pharmaceutically acceptable salt thereof.

11. A process according to claim 10, wherein R_{10} is an isopropylamino, tert.butylamino or o-methoxyphenoxyethylamino radical and R_1 is a mesyl radical.

12. A process for the preparation of an S-carbazole derivative of the formula (I):

B

and the pharmacologically compatible, pharmaceutically acceptable salts thereof, comprising:

reacting R-(-)-epichlorohydrin with 4-hydroxycarbazole in the presence of an organic solvent in an alkaline medium and,

reacting the S-4-(2,3-epoxypropoxy)-carbazole obtained with ammonia or substituted ammonia of the formula $R_{10}H$, in which R_{10} has the same meaning as above, whereafter the compound (I) obtained is, if desired, converted into a corresponding pharmacologically compatible, pharmaceutically acceptable salt thereof.

13. A process according to claim 12, wherein R_{10} is an isopropylamino, tert.butylamino or o-methoxyphenoxyethylamino radical.

18. A process according to claim 2, for preparing R-(+)-(1-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)]-ethylaminopropan-2-ol, comprising reacting R-(-)-4-(2,3-epoxypropoxy)-carbazole with o-methoxyphenoxyethylamine.

19. A process according to claim 10, for preparing R-(+)-(1-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)]-ethylaminopropan-2-ol, comprising reacting 4-hydroxycarbazole with S-(+)-3-mesyloxy-1,2-epoxypropane and reacting the R-(-)-4-(2,3-epoxypropoxy)-carbazole thus obtained, with o-methoxyphenoxyethylamine.

20. A process according to claim 3, for preparing S-(-)-(1-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)]-ethylaminopropan-2-ol, comprising reacting S-(+)-4-(2,3-epoxypropoxy)-carbazole with o-methoxyphenoxyethylamine.

21. A process according to claim 12, for preparing S-(-)-(1-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)]-ethylaminopropan-2-ol, comprising reacting 4-hydroxycarbazole with R-(-)-epichlorohydrin and reacting the S-(+)-4-(2,3-epoxypropoxy)-carbazole thus obtained with o-methoxyphenoxyethylamine.

or a pharmaceutically acceptable, pharmacologically compatible salt thereof.

23. An R- or S-carbazole derivative of formula (I), as defined in claim 22, or a pharmaceutically acceptable, pharmacologically compatible salt thereof, wherein R_{10} is amino.

24. An R- or S-carbazole derivative of formula (I), as defined in claim 22, or a pharmaceutically acceptable, pharmacologically compatible salt thereof, wherein R_{10} is isopropylamino, tert.-butylamino or o-methoxyphenoxyethylamino.

25. An R-carbazole derivative of formula (I), as defined in claim 22, or a pharmaceutically acceptable, pharmacologically compatible salt thereof.

26. An R-carbazole derivative of formula (I), as defined in claim 22, or a pharmaceutically acceptable, pharmacologically compatible salt thereof, wherein R_{10} is isopropylamino, tert.-butylamino or o-methoxyphenoxyethylamino.

27. An S-carbazole derivative of formula (I), as defined in claim 22, or a pharmaceutically acceptable, pharmacologically compatible salt thereof, wherein R_{10} is isopropylamino, tert.-butylamino or o-methoxyphenoxyethylamino.

34. A pharmaceutical composition containing an optically pure enantiomer of a derivative of formula (I), as defined in claim 22, an effective proportion of the other enantiomer of said derivative, said R- and S-enantiomers being present in a ratio of 1:99 to 99:1, but excluding the enantiomer ratio R:S of 50:50, and a pharmaceutically acceptable carrier.

35. A pharmaceutical composition according to claim 34, wherein said enantiomers comprise R-(+)- and S-(-)-(1-carbazol-4-yloxy)-3-[2-(2-methoxy-phenoxy)]-ethylaminopropan-2-ol.

36. A ß-blocking or blood pressure lowering pharmaceutical composition comprising a pharmaceutically effective amount of an R- or S-carbazole derivative of formula (I), or a pharmaceutically acceptable, pharmacologically compatible salt thereof, as defined in claim 22, 23 or 24, in association with a pharmaceutically acceptable carrier.

37. A ß-blocking or blood pressure lowering pharmaceutical composition comprising a pharmaceutically effective amount of an R-carbazole derivative of formula (I), or a pharmaceutically acceptable, pharmacologically compatible salt thereof, as defined in claim 25 or 26, in association with a pharmaceutically acceptable carrier therefor.

41. A ß-blocking or blood pressure lowering pharmaceutical composition comprising a pharmaceutically effective amount of S-(-)-(1-carbazol-4-yloxy)-3-[2-(2-methoxy-phenoxy)]-ethylaminopropan-2-ol in association with a pharmaceutically acceptable carrier.

42. A ß-blocking or blood pressure lowering pharmaceutical composition comprising a pharmaceutically effective amount of a non-racemic combination of R-(+)-(1-carbazol-4-yloxy)-3-[2-(2-methoxy-phenoxy)]-ethylaminopropan-2-ol and S-(-)-(1-carbazol-4-yloxy)-3-[2-(2-methoxy-phenoxy)]-ethylaminopropan-2-ol, said R- and S-enantiomers being present in a ratio of 1:99 to 99:1, but excluding the ratio of 50:50, in association with a pharmaceutically acceptable carrier.

F